REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claims 18-22 have been cancelled without prejudice or disclaimer as being directed to non-elected subject matter. Applicants reserve the right to file the subject matter of these claims in one or more continuing applications. Claims 1, 4 and 6 are currently being amended to recite that the LOH positive sample is further identified for use by a clinician for prognosis and treatment decisions. Claims 23-25 have been added. This amendment is fully supported by the originally-filed application, and specifically supported by paragraphs [0008], [0012], [0017] and [0039]. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier. After amending the claims as set forth above, claims 1-17 and 23-25 are now pending in this application. No new matter has been added.

1. Objections to the Specification

(a) The Examiner has objected to the embedded hyperlink in paragraph [0030] and reference to this site has been deleted as requested.

(b) In regard to the Examiner's request that underlining in the specification on pages 2 and 3 be deleted, applicants have reviewed 37 CFR 1.121(e)(2)(ii) and have found that this section refers to amendments and does not provide any prohibition against having underlined headings and subheadings in the specification. The cited section only applies to amendments. It is requested that the Examiner reconsider the basis for this objection and withdraw it.

2. The presently claimed invention is enabled and supported by the written description

Claims 8-17 are rejected under 35 U.S.C. § 112, first paragraph because, while the specification is enabling for a method for determining the likelihood of tumor reoccurrence in a patient previously diagnosed with a breast tumor or method of determining post-surgical

treatment for a breast cancer patient or method of identifying a patient as being at risk for breast cancer by analyzing breast tissue cell sample for loss of heterozygosity (LOH) at chromosomal locus 3p24.3, it allegedly "does not reasonably provide enablement for a method for determining the likelihood of tumor reoccurrence in a patient previously diagnosed with a breast tumor or method of determining post-surgical treatment for a breast cancer patient or method of identifying a patient as being at risk for breast cancer by analyzing a tissue cell sample for the level of expression of thyroid hormone receptor beta 1 (TRβ1) gene." According to the Examiner, the specification does not provide substantial data which supports the claims that the expression of the TRβ1 gene is indicative of a likelihood of breast tumor reoccurrence in a patient or indicative of identifying patients at risk for breast cancer. In support of applicants' position that the subject matter of claims 8-17 are enabled, applicants herewith provide a declaration under 37 CFR § 1.132 (Exhibit 1) by one of the inventors, Dr. Shanaz H. Dairkee. It is requested that the Examiner consider Dr. Dairkee's comments and information in regard to this rejection.

Applicants respectfully disagree with the Examiner's position and submit that the specification does provide sufficient evidence and guidance to support a determination that the specification does satisfy the enablement requirements. While the Examiner listed the factors for determining enablement as enumerated in *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988), and below is a discussion of the Wands factors:

a. Nature of the Invention

"Whether the specification would have been enabling as of the filing date involves consideration of the nature of the invention, the state of the prior art, and the level of skill in the art. The initial inquiry is into the nature of the invention, i.e., the subject matter to which the claimed invention pertains. The nature of the invention becomes the backdrop to determine the state of the art and the level of skill possessed by one skilled in the art." MPEP § 2164.05(a). The invention is directed to a method for determining the likelihood of tumor re-occurrence in a patient by providing, analyzing and classifying patient target samples to that have a lower level of expression of thyroid hormone receptor β1 (TRβ1) compared to a control cell sample. The invention therefore involves the well-known techniques of sample isolation, of RNA transcript or protein expression analysis using standard techniques well known to persons skilled in the art.

Therefore, the nature of the invention is such that the state of the art, and the level of skill in the art are very advanced, and therefore, the methods of claims 8-17 are enabled.

b. Breadth of the Claim

Claims 8-17 are directed to analyzing the level of expression of TRβ1 and comparing the level of expression with a control cell sample. Thus, the claims are directed to analyzing a specific gene, TRβ1, located at a particular chromosomal locus, 3p24.3, and are therefore not broader than the enabling disclosure of the specification.

c. The State of the Prior Art and the Predictability of the Art

The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839 (CCPA 1970), MPEP § 2164.03. Therefore, as the level of skill in the art and predictability of the relevant art increases, the requirement for detailed disclosure lowers. The Examiner has suggested that the data provided in the specification are speculative but Exhibit 1, paragraph 4, explains that the data is not speculative but that it is useful to identify a subset of breast tumors that may be triggered by the TRβ1 pathway.

The methods of determining the TRβ1 expression levels are well known in the relevant art, and skills of the artisans are highly developed so that the outcome or result of the method is reliable. Accordingly, because the amount of knowledge in the state of the art as well as the predictability in the art is high, the requirement for detailed disclosure is not as high.

d. The Presence or Absence of a Working Example and the Amount of Direction or Guidance Presented

"Compliance with the enablement requirement of 35 USC § 112, first paragraph, does not turn on whether an example is disclosed. An example may be 'working' or "prophetic. A working example is based on work actually performed. A prophetic example describes an embodiment of the invention based on predicted results rather than work actually conducted or results actually achieved. " MPEP § 2164.02.

The specification does not need to contain an example if the invention is otherwise sufficiently disclosed so that one skilled in the art can practice the invention without undue experimentation. MPEP § 2164.02. In the present application, a method for determining the

level of TRβ1 expression in a target cell sample is disclosed in paragraphs [0026] to [0033] and [0048] to [0057] and data is provided in Tables 5 and 6. This data are discussed in Exhibit 1, paragraph 5 and paragraph 6. Exhibit 1, paragraph 6, supports applicants position that the specification provides guidance to the skilled person to perform the methods of claims 8-17. Particularly, paragraph [0030] of the specification discloses how to develop standard values for TRβ1 expression levels and thus provides sufficient guidance. In view of this information, applicants submit that they have met the burden of showing that their specification provide sufficient guidance for the skilled person to perform the claimed method.

e. The Quantity of Experimentation Necessary

"The quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether 'undue experimentation' is required to make and use the invention. Time and difficulty of experiments are not determinative if they are merely routine." MPEP § 2164.06(a). The Examiner has stated that a large quantity of experimentation would be required by the skilled person to determine sample size and to monitor the patients over a period of years to obtain the relationship of TRβ1 expression to tumor reoccurrence. Office Action at page 6. However, applicants submit that such gathering of data and monitoring is not difficult and, in fact, are routine. Therefore, such experimentation would not be undue. As stated in the MPEP, above, routine experimentation is not undue experimentation.

Applicants have provided the necessary link between at 3p24.3 and the decrease of TRβ1 expression as noted by the Examiner. Office Action at page 4. Applicants also have provided in Exhibit 1, paragraphs 7 – 10 that show that TRβ1 expression is reduced by TRβ1 promoter methylation, and that higher levels of expression of TRβ1 inhibits growth of tumor cells and a non-malignant cell that has been developed as a model closely analogous to the genetically altered normal TDLU of cancerous breast tissue.

Applicants submit that they have provided the data which supports their position that lower levels of TRβ1 transcripts are correlated with LOH, and promoter methylation, and that higher levels of TRβ1 inhibit the growth of certain sub-populations of tumor cells as well as non-malignant cells that surround the breast tumor cells and which appear to be normal. In conjunction with our data on 3pLOH in normal TDLU and the increased risk of recurrence, it appears likely that partial or complete TRß1 inactivation in normal TDLU, which results in a

lower level of TRß1 transcript, enables the selection of cells in breast tissue, which are prone to the development of a new primary tumor. Thus the measurement of relative levels of TRß1 transcript or gene product in normal TDLU indicate the risk of tumor recurrence in a certain subset of breast cancers.

The sophistication of those of skill in the art combined with the detailed guidance provided in the specification, amply enables the claimed method. For these reasons, Applicants have overcome the enablement rejection. Accoordingly, applicants therefore respectfully request withdrawal of this rejection.

3. The present claims are not anticipated by, or alternatively obvious over Deng *et al.*

Claims 1-7 are rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as being unpatentable over Deng *et al.*, Science, Vol. 272, pages 2057-2059 (1996) because Deng *et al.*, allegedly teach a method comprising the steps of claims 1-7. Office Action at pages 7-8. In an effort to expedite prosecution and without acquiescing to the basis of the Examiner's rejection, applicants have amended claims 1, 4 and 6, to clarify the present invention by including a step that then identifies the LOH positive target sample to a clinician. In view of the amendment, it is requested that this rejection be withdrawn.

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

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Respectfully submitted,
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